EFFICACY OF FOOD INCLUDING 5,7-DIMETHOXYFLAVONE FOR OBESITY UNDER CONDITIONS OF A CERTAIN AMOUNT OF EXERCISE

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Abstract

Objective: The effects of food including 5,7-Dimethoxyflavone (NMC) for obesity under conditions of a certain amount of exercise were investigated with a placebo-controlled double-blind trial.
Methods: Healthy, slightly-obese Japanese men and women (30-59 years of age) were randomly assigned to two groups (n = 25). Each subject ingested 1 capsule of NMC or placebo and exercised lightly about 7 minuts every day for 12 weeks. Weight, body fat percentage, BMI, waist circumference, hip circumference and subjective symptoms were evaluated.
Results: The ingestion of NMC for 12 weeks significantly improved weight, body fat percentage, BMI, waist circumference and hip circumference relative to that of placebo group ($p < 0.01$). An intergroup analysis showed that the weight, body fat percentage, BMI, waist circumference and hip circumference decreased significantly in the NMC group ($p < 0.05$), but not in the placebo group. Subjective evaluations were not significantly changed in this study. No adverse effects attributable to MNC were observed.
Conclusions: These results suggests that the ingestion of MNC under conditions of a certain amount of exercise for 12 weeks improves obesity prevention and waist and hip circumferences.

Key words: 5,7-Dimethoxyflavone, obesity, black ginger

INTRODUCTION

In contemporary Japan, as the society that often allows excess intake of calories and irregular lifestyles, many people have a tendency to be distressed about their obesity. Obesity is a state of excessive body fat accumulation than a prescribed level, however, a visceral fat obesity that accumulates excessive fat around internal organs specially causes high cholesterol and blood sugar level, and even leads to serious arteriosclerosis at the end.[1] Consequently, obesity becomes a major risk factor of many diseases including so-called lifestyle diseases in reality, prevention and solution of obesity are expectation of many people in common.

Obviously, diet and exercise are essentials to prevention and solution of obesity, however, dietary supplements have also become one of effective measures for many people who have the same problem. And those supplements are made from variety of ingredient in accordance with its end effect and a role as a nutrition compensator, an appetite suppressor or a bowel movement promoter, so on. A black ginger is one of the kind.

A black ginger (*Kaempferia parviflora*) that is called 'kuro-shouga' (or black termeric), or 'krachaidam' in Thailand as a place of origin, has been known from ancient times as a nourishing Thai herb root to be boiled for drink when one has an arthralgia. It's been also said that it contains anthocyanin, methoxyflavone, selenium, amino acid and curcumin, however, above all of those, 5,7-Dimethoxyflavone as a largest portion of polymethooxyflavone must be the most essential element for black ginger.[2] Originally, 5,7-Dimethoxyflavone has been reported for its anti-inflammatory[3] and vasorelaxation actions,[4] however, black ginger extract itself that contains abundant 5,7-Dimethoxyflavone is said to be a major functional food element which works for improvements in bloodstream[5] and anti-obesity[6] as well.

Therefore, this report aimed to prove the anti-obesity effect of food that contains black ginger extract (5,7-Dimethoxyflavone) as a test material, to a group of healthy men and women including some light obese subject, along with a certain level of daily exercise as an obligation.

MATERIALS AND METHODS

1. Examining Bodies

This study was conducted by JACTA (Japan Clinical Trial Association, Tokyo) associated with Dr. Mitsuhiko Munekata. The measurements were carried out in both JACTA and OZ Clinic (Tokyo).

2. Subjects

The study participants were recruited by JACTA, and selected according to the following criteria.

Table 1 Components and Nutritional Constituents of the Test Samples

Components of NMC		Components of Placebo	
Ingredients	Quantity (mg)	Ingredients	Quantity (mg)
Vegetable Fat and Oil	129.2	Safflower Oil	230 mg
Black Ginger Extract	13.36		
Dextrin	13.32		
Cyclodextrin	13.32		
Ginger Extract Powder	36		
Black Pepper Extract	0.5		
Grape Seed Extract	0.3		
Beeswax	22		
Spice Extract	1		
Vitamin E	1		

Nutritional Constituents	NMC	Placebo
Energy	2.13 kcal	2.59 kcal
Protein	0.1 g	0.1 g
Fat	0.16 g	0.23 g
Carbohydrate	0.09 g	0.03 g
Sodium	0.34 mg	0.27 mg

Per 1 capsule 230 mg

Inclusion Criteria:

① Healthy adults aged 30-59 years

Exclusion Criteria:

① Who's BMI score is under 20
② Have a prior medical history of food allergy
③ Are taking hormonal therapy
④ Are in pregnancy or lactation
⑤ Are taking drugs that might affect the result
⑥ Are taking supplements or functional foods that might affect the result
⑦ Are judged to be unsuitable test subjects by the doctor responsible for the present study

The Ethics Committee and Informed Consent:

This study received the approval of the Institutional Review Board of LLP Pharmaceutical Law Wisdoms in accordance with the ethical standard established in the Helsinki declaration, and written and spontaneous informed consent was obtained from the subjects with written and oral explanation of the test objective and its method.

3. Test Materials

Test Food and Placebo:

The test food was 'Nenshou Meramera Capsule' (NMC), a food supplement containing black ginger extract (5,7-Dimethoxyflavone) (Supplier: Mizuhashihojyudo Pharmaceutical Inc), along with placebo without the black ginger extract (5,7-Dimethoxyflavone). Ingredients and nutrient composition of each are indicated in **Table 1**.

Intake Method:

The test subject were instructed to take 1 capsule, 1 time per day with water or tepid water, and also recommended to take it after supper, with proper regards for restraining carbohydrate intake.

4. Examination Method

Study Design:

Conducted a double-blind, placebo-controlled parallel group study.

Allocation of the Subjects:

An allocation manager who was not involved in the examination assigned the subjects to the test groups (25/25). The allocation status that had been severely kept during the test period by the allocation manager was eventually disclosed after fixation of the test results.

Test Schedule:

Table 2 indicates the test schedule. The test period was set between July and October, 2014; begun with acquisition of baseline data before examination, followed by regular ingestion of test materials for 12 consecutive weeks. The assay dates were set before ingestion, and after 4 weeks, 8 weeks and 12 weeks. A biochemical blood test and an urinalysis were conducted twice, before ingestion and after 12 weeks. The subjects were prohibited from engaging in alcohol consumption the night before, and asked to come to the clinic at the same time on each examination day after taking regular breakfast.

During the test period, they were also asked to engage in light exercise everyday. The exercise was instructed to pull back a belly for 10 sec. and relieve it for another 10 sec. during they are walking, and to repeat the motion

Table 2　Test Schedule

Item \ Term	Before Ingestion	Screening	Test Period (12 w)		
			After 4 w	After 8 w	After 12 w
Coming to Hospital	○		○	○	○
Informed Consent	○				
Selection of Applicants		○			
Subjective Evaluation	○		○	○	○
Physical Test	○		○	○	○
Blood Test	○				○
Urinalysis	○				○
Ingestion of Test Foods			⟷		
Diary	⟷				

○ : Implementation

⟷ : Daily practice during the test period

20 times (approx. 7 mins per day).They were also instructed not to take any other new supplements nor having excessive physical exercises and bulimia for daily standards. In order to confirm their observance of the rules, they were obliged to submit a diary that keeps daily records of their meals and total count of pedometers.

5. Examination Items

Evaluation of Effectiveness:

① Primary Outcome

The examiner in cooperation with 'Yamato Biospace Technology' (Yamato Scale Co., Ltd.) conducted physical measurements of weight, body fat percentage, BMI, waist circumference and hip circumference.

② Secondary Outcome

Subjective evaluations of the participants were conducted before and after 4, 8, 12 weeks of ingestion, questioning about their bowel movement, skin condition, physical condition in general and sleep, by showing 10-degree measurement scale from 0 (very bad) to 9 (very good) with 5 as a standard score before ingestion. **Fig.1** indicates the questionnaire.

Evaluation of Safety:

Items for safety evaluation were also added to secondary outcome.

① Biochemical Blood Test

The subjects were taken blood samples after 10 minute repose from their show ups. It examined in-blood levels of total bilirubin, total protein, albumen, AST (GOT), ALT (GPT), ALP, LD (LDH), γ-GT (γGTP), CK (CPK), total cholesterol, neutral fat (TG), sodium, chloride, potassium, calcium, inorganic phosphorus, urea nitrogen, creatinine, blood sugar (serum).

② Urinalysis

Urinalyses were conducted after the subjects show ups, examined urine protein, sugar, urobilinogen, keton body, occult blood, bilirubin (all of above are qualitative) and pH, specific gravity (both are quantitative).

Questionnaire

Test material

Name　　age

Item		Degree of Improvement								
Bowel Movement	0 w	1	2	3	4	⑤	6	7	8	9
	4 w	1	2	3	4	5	6	7	8	9
	8 w	1	2	3	4	5	6	7	8	9
	12 w	1	2	3	4	5	6	7	8	9
Skin Condition	0 w	1	2	3	4	⑤	6	7	8	9
	4 w	1	2	3	4	5	6	7	8	9
	8 w	1	2	3	4	5	6	7	8	9
	12 w	1	2	3	4	5	6	7	8	9
Physical Condition	0 w	1	2	3	4	⑤	6	7	8	9
	4 w	1	2	3	4	5	6	7	8	9
	8 w	1	2	3	4	5	6	7	8	9
	12 w	1	2	3	4	5	6	7	8	9
Sleep	0 w	1	2	3	4	⑤	6	7	8	9
	4 w	1	2	3	4	5	6	7	8	9
	8 w	1	2	3	4	5	6	7	8	9
	12 w	1	2	3	4	5	6	7	8	9

● Your impression after 4 wks? (Name anything you might feel to be different from what it was before.)

● Your impression after 8 wks? (Name anything you might feel to be different from what it was before.)

● Your impression after 12 wks? (Name anything you might feel to be different from what it was before.)

Fig. 1　Questionnaire for Subjective Evaluation

③ Diary

The subjects life customs and adverse events were evaluated with examination using diary.

Statistical Processing:

Measured values of each evaluation items were indicated in Mean ± SD. As for measured values from physical evaluation, paired t-test was conducted for intragroup comparison, and repeated-measures ANOVA was for intergroup comparison. For subjective evaluations,

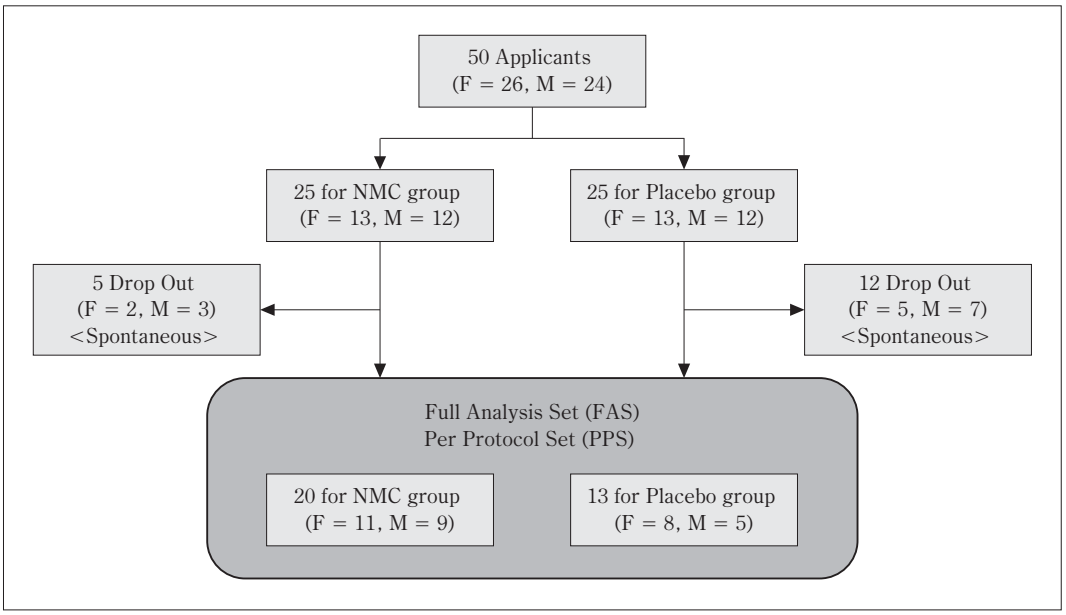

Fig. 2 Screening Process of the Subjects

Table 3 Subjects Demographics (PPS)

Item	Unit	NMC	Placebo	Total PPS
Number*	psn.	20	13	33
Gender (F/M)*	psn.	11/9	8/5	19/14
Age	Yr.	47.8 ± 6.0	48.2 ± 5.3	47.9 ± 5.7
Height	cm	163.0 ± 6.4	163.3 ± 6.9	163.1 ± 6.5
BMI	kg/m^2	25.8 ± 3.2	24.6 ± 3.6	25.3 ± 3.4

*Total number of subjects
Mean ± SD.
No significant difference

Wilcoxon signed-rank test was for intragroup comparison. Mann-Whitney U test was for intergroup comparison. For safety evaluation, paired t-test was for intragroup comparison. And Student's t-test was for intergroup comparison. For measurements of deviation in the subjects background, Student's t-test was conducted. The significant level used was the 95% confidence level ($p < 0.05$). Statcel 3 (Yanai, 2011) as a statistical analysis application was used for those evaluations.

RESULTS

Fig.2 indicates the process for screening the subjects. The test commenced after selecting 50 candidates based upon both inclusion and exclusion criteria, then allocate 25 subjects. (F = 13, M = 12) to the NMC group and another 25. (F = 13, M = 12) to the placebo group. Consequently, total of 17 (5 out of the NMC group, 12 out of the placebo group) amongst the 50 subjects were dropped. Then, 1 amongst the dropouts (the NMC group) spontaneously quitted due to physical deconditioning, and the rest of 16 were spontaneously quitted for other reasons to make the continuation unable, such as work-related issues. Total of 33 subjects (20 out of the NMC group and 13 out of the placebo group) completed the whole 12 wks test (FAS). In both groups, there were no subject who corresponded to the exclusion standard, therefore, the per protocol set (PPS) were eventually 33 in total (age 47.9 ± 5.7 yr, height 163.1 ± 6.5 cm, BMI 25.3 ± 3.4 kg/m^2). In detail, there were 20 out of the NMC group (age 47.8 ± 6.0 yr, height 163.0 ± 6.4 cm, BMI 25.8 ± 3.2 kg/m^2) and 13 out of the placebo group (age 48.2 ± 5.3 yr, height 163.3 ± 6.9 cm, BMI 24.6 ± 3.6 kg/m^2). **Table 3** indicates demographic background of those test subjects. Between those two groups, there were no significant difference observed in gender, age, height, and BMI.

Table 4 shows changes in anthropometric parameters. Weight, body fat percentage, BMI, waist circumference and hip circumference after 12 wks were significantly different between the NMC group and the placebo group analyzed by repeated-measures ANOVA.

Table 5 indicates transition of the measured values of subjective evaluations. It indicates that the scores for both groups had no significant change in transition from before

Table 4　Transition of Physical Values (NMC; N = 20, Placebo; N = 13)

Item	Unit	Group	0 w	12 w[1)]	p-value[2)]
			Mean ± SD	Mean ± SD	Time × group
Weight	kg	NMC Placebo	69.23 ± 12.60 66.03 ± 12.26	65.81 ± 12.14** 66.52 ± 12.38	< 0.01 ##
Body Fat Percentage	%	NMC Placebo	32.4 ± 6.9 30.9 ± 7.2	30.6 ± 6.7** 31.2 ± 7.5	< 0.01 ##
BMI	kg/m^2	NMC Placebo	25.8 ± 3.2 24.6 ± 3.6	24.6 ± 3.1** 24.8 ± 3.7	< 0.01 ##
Waist Circumference	cm	NMC Placebo	88.4 ± 8.3 85.2 ± 12.2	85.6 ± 8.3** 85.7 ± 12.6	< 0.01 ##
Hip Circumference	cm	NMC Placebo	95.4 ± 5.3 96.1 ± 7.1	93.5 ± 5.5** 96.2 ± 7.2	< 0.01 ##

1) **p < 0.01 vs. baseline (0w) (paired t-test)

2) ## p < 0.01 (repeated-measures ANOVA)

Table 5　Transition of Subjective Evaluation (NMC; N = 21, Placebo; N = 19)

Item	Group	12 w[1)]	p-value[2)]
		Mean ± SD	
Bowel Movement	NMC Placebo	5.5 ± 1.1 5.0 ± 0.9	p = 0.29
Skin Condition	NMC Placebo	5.0 ± 1.0 5.4 ± 1.4	p = 0.63
Physical Condition	NMC Placebo	5.5 ± 1.3 5.5 ± 1.3	p = 0.97
Sleep	NMC Placebo	5.3 ± 1.2 5.7 ± 1.0*	p = 0.41

Unit: Point

1) *p < 0.05 vs. baseline (0w) (Wilcoxon signed-rank test)

2) vs. Placebo group (Mann-Whitney U test)

ingestion to after 12 wks.

Table 6 indicates transition of the measured values of biochemical blood test. For both group, there were several significant changes. They were deemed just temporary, and most of them were remained within levels of the reference values. Plus, even those values except γ-GT (γGTP) (for men) and calcium, there were no significant difference between those two groups. Regarding changes of γ-GT (γGTP) (for men) and calcium, the doctor in charge judged as noncritical in clinical term, for its variance within the normal range.

Table 7 indicates transition of the measured values of urinalysis. For the NMC group, there were significant change in specific gravity in intragroup, however, it deemed as temporary and still within a level of reference value. In the placebo group, those two scores had no significant changes in intragroup and intergroup. As for urine protein, sugar, urobilinogen, keton body, occult blood and bilirubin items, no specific critical finding was observed in qualitative evaluation. (Data not shown) The doctor in charge judged that there should be no problem from clinical stand point.

As a result of evaluation of the diary, there were no critical adverse event observed in this test at all.

DISCUSSION

A double-blind, placebo-controlled parallel group study in total of 12 weeks, testing black ginger extract (5,7-Dimethoxyflavone) was conducted to healthy adults including light obese subjects (PPS: N = 33, age 47.9 ± 5.7, BMI 25.3 ± 3.4 kg/m^2), along with an instruction to have 7 minute exercise pulling back their bellies everyday. As a result, there were no significant improvement in subjective evaluation, however, weight, body fat percentage, BMI, waist circumference, hip circumference were equally showed improvements after

Table 6 Transition of Biochemical Blood Test (NMC; N = 20, Placebo; N = 13)

Item	Unit	Std. Value	Gender	Group	0 w	12 w[1)2)]
					Mean ± SD	Mean ± SD
Total Bilirubin	mg/dL	0.2-1.2	M/F	NMC Placebo	0.80 ± 0.48 0.70 ± 0.31	0.77 ± 0.49 0.65 ± 0.24
Total Protein	g/dL	6.5-8.3	M/F	NMC Placebo	7.3 ± 0.3 7.4 ± 0.4	7.2 ± 0.3 7.5 ± 0.4
Albumen	g/dL	3.8-5.3	M/F	NMC Placebo	4.5 ± 0.3 4.7 ± 0.2	4.4 ± 0.3* 4.6 ± 0.2 †
AST (GOT)	U/L	8-38	M/F	NMC Placebo	21.1 ± 5.6 22.7 ± 8.1	21.5 ± 5.5 19.8 ± 3.6
ALT (GPT)	U/L	4-43	M/F	NMC Placebo	19.5 ± 11.0 23.8 ± 15.0	21.6 ± 11.3 21.6 ± 10.2
ALP	U/L	110-354	M/F	NMC Placebo	201.7 ± 64.1 194.3 ± 47.7	208.2 ± 59.8 195.6 ± 48.5
LD (LDH)	U/L	121-245	M/F	NMC Placebo	196.7 ± 26.7 204.1 ± 88.3	186.2 ± 17.9* 169.6 ± 31.4 †
γ-GT (γ GTP)	U/L	86 and under	M	NMC Placebo	49.4 ± 62.9 74.6 ± 46.8	47.4 ± 55.0]# 54.4 ± 32.8*]
		48 and under	F	NMC Placebo	19.0 ± 10.6 22.0 ± 6.9	19.8 ± 9.4 24.8 ± 8.2 †
CK (CPK)	U/L	38-196	M	NMC Placebo	164.9 ± 115.7 160.0 ± 103.7	125.6 ± 42.0 114.4 ± 75.7
		30-172	F	NMC Placebo	153.3 ± 166.9 91.5 ± 33.7	162.6 ± 259.4 89.3 ± 34.1
Total Cholesterol	mg/dL	130-219	M/F	NMC Placebo	213.6 ± 38.8 209.4 ± 36.3	209.7 ± 36.3 198.9 ± 32.0
Neutral Fat (TG)	mg/dL	30-149	M/F	NMC Placebo	146.2 ± 90.4 245.8 ± 295.5	121.3 ± 75.2 140.4 ± 81.5
Sodium	mEq/L	135-150	M/F	NMC Placebo	140.1 ± 2.2 139.1 ± 2.3	141.8 ± 3.3* 142.8 ± 3.4**
Chloride	mEq/L	98-110	M/F	NMC Placebo	104.1 ± 2.0 102.9 ± 1.7	104.5 ± 1.6 103.9 ± 1.7 †
Potassium	mEq/L	3.5-5.3	M/F	NMC Placebo	6.6 ± 1.0 7.0 ± 1.2	4.4 ± 0.5** 4.5 ± 0.6**
Calcium	mg/dL	8.4-10.2	M/F	NMC Placebo	9.5 ± 0.3 9.5 ± 0.3	9.3 ± 0.3*]## 9.5 ± 0.4]
Inorganic Phosphorus	mg/dL	2.5-4.5	M/F	NMC Placebo	3.1 ± 0.4 3.3 ± 0.4	3.1 ± 0.6 3.5 ± 0.5
Urea Nitrogen	mg/dL	8.0-22.0	M/F	NMC Placebo	14.3 ± 2.7 12.7 ± 2.6	12.8 ± 2.7* 12.3 ± 3.0
Creatinine	mg/dL	0.61-1.04	M	NMC Placebo	0.80 ± 0.16 0.81 ± 0.17	0.80 ± 0.15 0.90 ± 0.13
		0.47-0.79	F	NMC Placebo	0.67 ± 0.09 0.63 ± 0.09	0.68 ± 0.11 0.66 ± 0.08
Blood Sugar (Serum)	mg/dL	60-109	M/F	NMC Placebo	55.4 ± 20.6 60.0 ± 12.0	71.2 ± 14.9** 74.3 ± 13.0**

1) †$p < 0.1$, *$p < 0.05$, **$p < 0.01$ vs. baseline (0w) (paired t-test)

2) #$p < 0.05$, ##$p < 0.01$ vs. Placebo group (Student's t-test)

Table 7　Transition of Urinalysis (NMC; N = 20, Placebo; N = 13)

Item	Unit	Std. Value	Gender	Group	0 w	12 w
					Mean ± SD	Mean ± SD
Specific Gravity	mg/dL	1.0102-1.025	M/F	NMC Placebo	1.0227 ± 0.0072 1.0362 ± 0.05	1.0177 ± 0.0049** 1.0177 ± 0.0044
pH	g/dL	4.5-8.0	M/F	NMC Placebo	6.1 ± 0.7 6.4 ± 0.9	6.1 ± 0.8 5.8 ± 0.7 †

† $p < 0.1$, **$p < 0.01$ vs. baseline (0w) (paired t-test)

12 wks in the NMC group, against the placebo group. Looking at the change of the group, all of weight, body fat percentage, BMI, waist circumference, hip circumference showed constant improvements after 12 wks as well.

For working mechanism, black ginger extract (5,7-Dimethoxyflavone) in the test material has been reported to have various effects on improvement of an anti-inflammatory act or bloodstream, however, it's been also reported to be a pancreatic lipase inhibitor at the same time.[7] Therefore, ingested fat during the test period might have been hardly accumulated in subjects bodies.

In addition, accumulated fats are used as an important organ for energy expenditure through thermogenesis by increasing cAMP that is caused by binding blood adrenalin to the receptor of the fat cell surface, by activating hormone-sensitive lipase and by breaking down into fatty acids and glycerol.[8] Black ginger extract (5,7-Dimethoxyflavone) is reported to activate hormone-sensitive lipase or suppress the effect of body fat accumulation by working as inhibitor of phosphodiesterase (PDE), by breaking down cAMP and by raising cAMP density.[9]

Furthermore, black ginger extract (5,7-Dimethoxyflavone) is reported to increase the expression levels of the uncoupling protein-1 (UCP1) in mitochondria of brown adipose tissue that is considered to play an important role in activity of hormone-sensitive lipase.[10] Although it was reported in mice, recently the other study reported that brown adipose tissue are found on the human adults existing of brown adipose tissue have been suspected thereby useful food products promotes activating brown adipose tissue and increasing UCP1, to reduce obesity.[11] Therefore, in this study black ginger extract (5,7-Dimethoxyflavone) was suggested to work as some irritation for brown adipose tissue hyperactivity in the human body. However, it is only speculative and therefore is to be hoped that future research will clarify this point.

Also, black ginger extract (5,7-Dimethoxyflavone) such as above of functionality as well as ginger extract powder contained in the test products which is reported to raise metabolism or improve blood flow,[12][13] and black pepper extract which is reported to increase the absorption of ingested together raise metabolism and influence[14][15] are also considered to lead the test results supplementarily. However, these interactions are unknown and are an issue in the future.

And in this study, because the subjects were obliged to have daily 7 minutes exercise pulling back their bellies beside ingestion of the food, it might have affected the result as well.

Under the circumstance, it is suggested that those significant differences between two groups in weight, body fat percentage, BMI, waist circumference, hip circumference were aided by the exercise to some extent, however, we would like to work on this issue further.

And also in this study, there were no significant difference in subjective evaluation of bowel movement and skin condition, however, it could be explained as absence of the problem with their bowel movement and skin condition before the test, therefore, they could hardly feel the difference. Or simply, the test material itself could hardly have either positive or negative effects on those bowel movement and skin condition in any sense.

In summary, the test food was thought to be safe, since there were no chance to observe any adverse event which might caused by the food through the whole 12 week test period.

CONCLUSION

A placebo-controlled parallel group study testing 'Nensho Meramera Capsule' that contains black ginger extract (5,7-Dimethoxyflavone), under conditions of a certain amount of exercise, has proven significant improvements in general obesity prevention and partial body structure such as waist circumference and hip circumference in specific.

CONFLICT OF INTEREST

This research and its thesis authoring have been conducted by request of Mizuhashihojyudo Pharmaceutical Inc with their financial aid.

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